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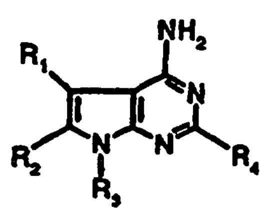
(54) Title: NOVEL PYRROLO[2,3-D]PYRIMIDINES AND THEIR USE AS TYROSINE KINASE INHIBITORS



(I)

(57) Abstract

Described are pyrrolo[2,3-d]pyrimidines of formula (I) wherein R_1-R_4 are as defined in the description. The compounds have valuable pharmaceutical properties and are effective especially as tyrosine protein kinase inhibitors. They can be used in warm-blooded animals in the treatment of bone diseases and other diseases that can be favourably influenced by the inhibition of tyrosine protein kinase.

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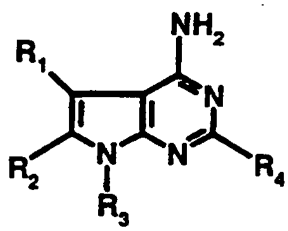
NOVEL PYRROLO (2,3-D) PYRIMIDINES AND THEIR USE AS TYROSINE KINASE INHIBITORS

The invention relates to compounds of formula I



(I)

wherein

R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;

and to salts thereof, to processes for the preparation of those compounds, to pharmaceutical compositions comprising those compounds, to the use of those compounds in the therapeutic treatment of the human or animal body or in the preparation of pharmaceutical compositions.

Within the context of the present Application, the general terms used hereinbefore and hereinafter preferably have the following definitions:

The prefix "lower " denotes a radical having up to and including 7, and especially up to and including 6, carbon atoms.

Lower alkyl is, for example, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl or *n*-heptyl, preferably ethyl or methyl.

Lower alkylene is, for example, methylene, ethylene or propylene, preferably methylene or ethylene.

Halogen is, for example, chlorine, bromine or fluorine, but may also be iodine.

Halo-lower alkyl is, for example, halomethyl, for example chloromethyl, or, for example, trifluoromethyl.

Lower alkanoyl is, for example, acetyl, propionyl or pivaloyl, but may also be, for example, formyl.

Lower alkoxy is, for example, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, *n*-amyloxy or isoamyloxy, preferably methoxy or ethoxy.

Lower alkoxycarbonyl denotes the radical lower alkyl-O-C(O)- and is, for example, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, isobutoxycarbonyl, *sec*-butoxycarbonyl, *tert*-butoxycarbonyl, *n*-amyloxycarbonyl or isoamyloxycarbonyl, preferably methoxycarbonyl or ethoxycarbonyl.

Lower alkylamino is, for example, *n*-propylamino, *n*-butylamino, isopropylamino or isobutylamino, preferably methylamino or ethylamino.

Di-lower alkylamino is, for example, dimethylamino, diethylamino, di-*n*-propylamino, *n*-butylamino, di-*n*-butylamino or *n*-propyl-*n*-butylamino, preferably dimethylamino, diethylamino or methylethylamino.

Aryl is, for example, phenyl or naphthyl, each of which is unsubstituted or substituted, for example as indicated hereinafter for phenyl. Aryl is preferably phenyl unsubstituted or substituted by one or more, for example from one to three, especially one or two, substituents from the group consisting of lower alkyl, halo-lower alkyl, (hydroxy or lower alkanoyloxy)-lower alkyl, lower alkoxy-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkyl, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkyl, (amino or lower alkanoylamino)-lower alkyl, lower alkylamino-lower alkyl,

di-lower alkylamino-lower alkyl; azacycloalkyl-lower alkyl, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkyl; azaheteroaryl-lower alkyl, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower alkyl, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkyl; azacycloalkyl-lower alkylamino-lower alkyl, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkylamino-lower alkyl; azaheteroaryl-lower alkylamino-lower alkyl, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkylamino-lower alkyl; mercapto-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, aminocarbonyl-lower alkyl, N-lower alkylaminocarbonyl-lower alkyl, N,N-di-lower alkylaminocarbonyl-lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, C_1-C_3-alkylenedioxy, phenyl-lower alkoxy, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy, (amino or lower alkanoylamino)-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy; azacycloalkyl-lower alkoxy, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkoxy; azaheteroaryl-lower alkoxy, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkoxy; (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkoxy; azacycloalkyl-lower alkylamino-lower alkoxy, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkylamino-lower alkoxy; azaheteroaryl-lower alkylamino-lower alkoxy, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkylamino-lower alkoxy; (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkoxy, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkoxy, hydroxysulfonyl-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, aminocarbonyl-lower alkoxy, N-lower alkylaminocarbonyl-lower alkoxy, N,N-di-lower alkylaminocarbonyl-lower alkoxy, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino; azacycloalkyl, for example piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl; azaheteroaryl, for example imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl; mercapto, lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or

sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkyl-(thio, sulfinyl or sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower alkyl-(thio, sulfinyl or sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkyl-(thio, sulfinyl or sulfonyl), carboxy-lower alkylthio, lower alkoxycarbonyl-lower alkylthio, aminocarbonyl-lower alkylthio, N-lower alkylaminocarbonyl-lower alkylthio, N,N-di-lower alkylaminocarbonyl-lower alkylthio, halogen, carboxy, lower alkoxycarbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N-[(hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl]-aminocarbonyl, N-[(amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl]-aminocarbonyl; [azacycloalkyl-lower alkyl]-aminocarbonyl, for example N-[(piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkyl]-aminocarbonyl; [azaheteroaryl-lower alkyl]-aminocarbonyl, for example N-[(imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkyl]-aminocarbonyl; N-(hydroxysulfonyl-lower alkyl)-aminocarbonyl, N,N-di-lower alkylaminocarbonyl, cyano, amidino, formamidino and guanidino and, for example, nitro, lower alkanoyl and benzoyl.

Hydroxysulfonyl is the group $-SO_3H$. Aminocarbonyl is $-CONH_2$. Amidino is $-C(=NH)-NH_2$. Formamidino is $-NH-CH(=NH)$ and guanidino is $-NH-C(=NH)-NH_2$.

Cyclo-lower alkyl is an aliphatic ring having preferably from 3 up to and including 7 ring members, such as cyclopropyl, cyclobutyl, cycloheptyl, and especially cyclopentyl or cyclohexyl.

Cyclo-lower alkenyl is a mono- or, optionally, poly-unsaturated ring having preferably from 3 up to and including 7 ring members, such as cycloprop-1-enyl, cycloprop-2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, cyclopent-3-enyl, cyclopenta-1,3-dienyl, cyclohex-1-enyl, cyclohexa-1,3-dienyl or cyclohept-2-enyl, especially cyclopent-2-enyl.

Cyclo-lower alkyl and cyclo-lower alkenyl are unsubstituted or substituted by one or more, for example, depending on the size of the ring, from one to four, especially one, two or three, substituents from the group consisting of hydroxy, oxo, lower alkanoyloxy, hydroxy-

lower alkyl, lower alkanoyloxy-lower alkyl, carboxy, amino, lower alkanoylamino, amino-lower alkyl, lower alkanoylamino-lower alkyl, carbonyl-lower alkoxy, hydroxy-lower alkyloxy, lower alkanoyloxy-lower alkyloxy, lower alkoxy-lower alkoxy, amino-lower alkoxy, lower alkanoyl-amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, imidazolyl-lower alkoxy, triazolyl-lower alkoxy, tetrazolyl-lower alkoxy, hydroxy-lower alkylamino, hydroxy-lower alkylamino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, azacycloalkyl-lower alkyl, hydroxy-lower alkyl-aminocarbonyl, lower alkyl-amino-carbonyl, di-lower alkyl-aminocarbonyl, azacycloalkylcarbonyl, lower alkanoyloxy-lower alkylamino, lower alkoxy-lower alkylamino, amino-lower alkylamino, lower alkanoylamino-lower alkylamino, lower alkylamino-lower alkylamino, di-lower alkylamino-lower alkylamino, imino, lower alkylimino, hydroxy-lower alkylimino, lower alkoxy-lower alkylimino, imidazolyl-lower alkylamino, triazolyl-lower alkylamino and tetrazolyl-lower alkylamino. Two ring atoms can additionally be linked to one another *via* an oxy-lower alkyleneoxy radical.

In substituents containing groups such as, for example, hydroxy-lower alkoxy, amino-lower alkoxy, hydroxy-lower alkylamino, amino-lower alkylamino, hydroxy-lower alkylthio or amino-lower alkylthio, the two hetero atoms are preferably separated from one another by at least two carbon atoms; in other words, the lower alkyl moiety is preferably so selected that there are at least two carbon atoms between the two hetero atoms.

Azacycloalkyl is a cycloalkyl radical having from 3 to 8, especially from 5 to 7, ring atoms, at least one of the ring atoms being a nitrogen atom. Azacycloalkyl may also contain further ring hetero atoms, for example N, O or S; it is, for example, piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl.

Azaheteroaryl is an aromatic radical having from 3 to 7, especially from 5 to 7, ring atoms, at least one of the ring atoms being a nitrogen atom. Azaheteroaryl may also contain further ring hetero atoms, for example N, O or S. It may also be partially saturated. Azaheteroaryl is, for example, imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl.

Radicals such as piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, imidazolyl, triazolyl and pyrrolyl can be bonded *via* a ring nitrogen atom or a ring carbon atom, and radicals such as pyridyl or pyrimidinyl are preferably bonded *via* a carbon atom.

The azacycloalkyl radicals bonded *via* a ring nitrogen atom, which are preferred, are referred to in known manner as piperidino, piperazino, morpholino, pyrrolidino, etc..

Salts of compounds of formula I are especially pharmaceutically acceptable salts, especially acid addition salts with suitable mineral acids, such as hydrohalic acids, sulfuric acid or phosphoric acid, for example hydrochlorides, hydrobromides, sulfates, hydrogen sulfates or phosphates, salts with suitable aliphatic or aromatic sulfonic acids or N-substituted sulfamic acids, for example methanesulfonates, benzenesulfonates, p-toluenesulfonates or N-cyclohexylsulfamates (cyclamates), or salts with strong organic carboxylic acids, such as lower alkanecarboxylic acids or saturated or unsaturated or hydroxylated aliphatic dicarboxylic acids, for example acetates, oxalates, malonates, maleates, fumarates, tartrates or citrates.

Also possible, where the compounds of formula I contain an acid group, are corresponding salts with bases, for example corresponding alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, pharmaceutically acceptable transition metal salts, such as zinc or copper salts, or salts with ammonia or organic amines, such as cyclic amines, mono-, di- or tri-lower alkylamines, hydroxy-lower alkylamines, for example mono-, di- or tri-hydroxy-lower alkylamines, hydroxy-lower alkyl-lower alkyl-amines or polyhydroxy-lower alkylamines. Cyclic amines are, for example, morpholine, thiomorpholine, piperidine or pyrrolidine. Suitable mono-lower alkylamines are, for example, ethyl- and *tert*-butyl-amine; suitable di-lower alkylamines are, for example, diethyl- and diisopropyl-amine and suitable tri-lower alkylamines are, for example, trimethyl- and triethyl-amine. Suitable hydroxy-lower alkylamines are, for example, mono-, di- and tri-ethanolamine; suitable hydroxy-lower alkyl-lower alkyl-amines are, for example, N,N-dimethylamino- and N,N-diethylamino-ethanol. Compounds of formula I having an acid group, for example carboxy, and a basic group, for example amino, may also be in the form of, for example, internal salts, i.e. in zwitterionic form, or part of the molecule may be in the form of an internal salt and another part in the form of a normal salt. Pharmaceutically unacceptable salts are also included, since they can be used, for example, for the isolation and/or purification of free compounds I and the pharmaceutically acceptable salts thereof.

The compounds of formula I have valuable pharmacological properties. In particular, they inhibit the activity of tyrosine protein kinase $pp60^{c\text{-}src}$ in concentrations of from approximately 0.001 to approximately 10 µM [test description: K. Farley *et al.*, *Anal. Biochem.* **203** (1992) 151-157; purified enzyme - as described in N. B. Lydon *et al.*, *Biochem. J.* **287** (1992) 985-993 - is used].

It is known that both targeted modification of the c-src gene leading to the elimination of c-src and inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$ affect the bone absorption ability of osteoclasts [for elimination of c-src by gene manipulation: see, for example, P. Soriano *et al.*, *Cell* **64** (1991) 693-702; for inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$: see, for example, B.F. Boyce *et al.*, *J. Clin. Invest.* **90** (1992) 1622-1627; T. Yoneda *et al.*, J. Clin. Invest. 91 (1993) 2791-2795].

Owing to their inhibitory activity against tyrosine protein kinase $pp60^{c\text{-}src}$, the compounds of formula I are therefore capable of inhibiting the bone absorption ability of osteoclasts. That can be demonstrated, for example, in the bone slice assay on bovine cortical bone platelets with rat osteoclasts in concentrations of from approx. 0.001 to approx. 10 µM. [The "bone slice assay" is described, for example, in *Biochem. Biophys. Res. Comm.* **188** (1992) 1097-1103]. In that assay, the compounds of formula I inhibit the formation of characteristic absorption holes in bone platelets *in vitro.*

In vivo, the effectiveness of compounds of formula I can be demonstrated, for example, in the Hock model in the rat. In that test, the compounds of formula I - when administered once a day *per os* in concentrations of from approx. 1 to approx. 100 mg/kg of body weight - for from 3 to 4 weeks completely or at least partially inhibit the bone loss produced as a result of ovariectomy in rats [the "Hock model" is described, for example, in *Metab. Bone Dis.* **5** (1984) 177-181].

The *in vivo* activity of compounds of formula I can also be demonstrated, for example, *via* calcium metabolism in intact rats. In that method, after i.v. injection of the test compound acute hypocalcaemia is induced within from 1 to 4 hours; it is demonstrated by determining the concentration of calcium in the blood plasma. The observation of acute hypocalcaemia can be interpreted as indirect evidence that the test compound inhibits bone absorption.

The compounds of formula I are therefore very suitable for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$. Special mention may be made here of osteoporosis, and of other diseases in the course of which the absorption of bone by osteoclasts plays a role, such as tumour-induced hypercalcaemia or Paget's disease, or the treatment of bone metastases, and also inflammatory processes in joints and bones and degenerative processes in cartilage tissue. In addition, the compounds of formula I are useful in the treatment of benign or malignant tumours that respond to inhibition of tyrosine protein kinase $pp60^{c\text{-}src}$, such as breast cancer (mammary carcinoma) or intestinal cancer (colon carcinoma). They are capable of effecting tumour regression and of preventing the formation of tumour metastases and the growth of micrometastases. The compounds of formula I are also useful in the treatment of cardiovascular diseases, such as thrombosis.

The compounds of formula I also inhibit the activity of other non-receptor tyrosine protein kinases, such as (a) other members of the src family, for example lck and fyn, (b) Abl kinase and (c) ZAP70 kinase. Furthermore, the compounds of formula I also inhibit the activity of receptor tyrosine protein kinases, such as (a) the EGF family, for example the EGF receptor, c-erbB2, c-erbB3 and c-erbB4, and (b) the PDGF family, for example the PDGF receptor, CSF-1, Kit, VEGF and FGF. Owing to those actions, the compounds of formula I can also be used in immunomodulation and in the treatment of diseases of the immune system, for example in the case of inflammations or organ transplants. They are also suitable for the treatment of (hyper)proliferative diseases, such as psoriasis, tumours, carcinomas and leukaemias, and in fibrosis and restenosis. The compounds of formula I can also be used in the treatment of diseases of the central or the peripheral nervous system where signal transmission by at least one tyrosine protein kinase is involved.

The invention relates especially to compounds of formula I wherein
R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;
R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

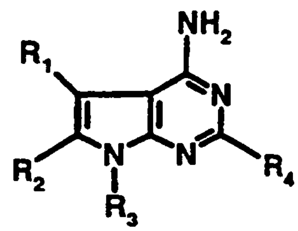
R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl, with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that in the 1-position radical must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;
and to salts thereof.

The invention relates more especially to compounds of formula I wherein
R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;
R_2 and R_4 are hydrogen; and
R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl, with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;
and to salts thereof.

Above all, the invention relates to compounds of formula I wherein
R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;
R_2 and R_4 are hydrogen; and
R_3 is unsubstituted or substituted cyclopropyl, cyclopentyl, cyclopentenyl or cyclohexyl, with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;
and to pharmaceutically acceptable salts thereof.

The invention relates especially to the specific compounds described in the Examples and to salts thereof.

The invention relates further to the use of compounds of formula I



(I)

wherein

R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl;

or pharmaceutically acceptable salts thereof,

in the preparation of a medicament for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase $pp60^{c-src}$.

The invention relates preferably to the use of compounds of formula I

wherein R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

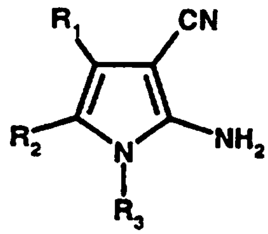
R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl and hydrocarbyloxycarbonylaminoalkyl;

or pharmaceutically acceptable salts thereof.

The compounds of formula I can be prepared in a manner known *per se*, for example by

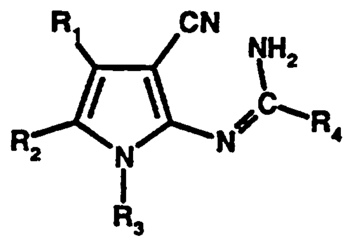
(a) subjecting a compound of formula II



(II)

to a ring-closure reaction with formation of the pyrimidine ring, or

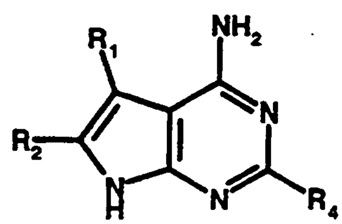
(b) subjecting a compound of formula III



(III)

to a ring-closure reaction with formation of the pyrimidine ring, or

(c) reacting a compound of formula IV



(IV)

with a compound of formula V

$$R_3\text{—}X \quad (V)$$

wherein X is a leaving group, or

(d) reacting a compound of formula IV with a compound that can be converted into a radical R_3, such as a cycloalkane epoxide, cycloalkene epoxide, cycloalkene or cycloalk-1-en-3-one,

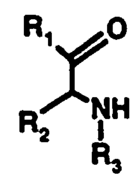
and, if desired, converting a compound of formula I into a different compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into a different salt,

and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.

In the more detailed description of the processes that follows, unless otherwise indicated each of the symbols R_1 to R_3 is as defined for formula I.

Process (a): The reaction according to process (a) corresponds to the cyclisation known *per se* of 2-amino-3-cyano-pyrroles to 4-amino-pyrrolo[2,3-d]pyrimidines (see, for example, H. Pichler *et al.*, *Liebigs Ann. Chem.* **1986**, 1485-1505). Suitable cyclisation reagents are, for example, (1) formamide or (2) 1. trialkyl orthoformate/2. ammonia. The cyclisation of compounds of formula II with formamide is preferably carried out at elevated temperature, for example at 160°C, and advantageously with the addition of a small amount of dimethylformamide and formic acid. The reaction of compounds of formula II with (a) trialkyl orthoformate(s) to give the corresponding alkoxy formimidates formed as intermediates normally takes place at less elevated temperatures, for example at from 80 to 120°C. The cyclisation of the latter with ammonia is then generally carried out again at relatively high temperatures, for example at 130°C in an autoclave.

The compounds of formula II are preferably prepared using one of the known methods of pyrrole synthesis. They are obtained, for example, by reacting a compound of formula IIa



(IIa)

with malonic acid dinitrile, preferably in the presence of a base, for example sodium ethanolate/ethanol.

The compounds of formula IIa can themselves be prepared, for example, by reacting a compound R_1-C(=O)-CH(-R_2)-Hal [Hal = halogen], that is to say, for example, phenacyl bromide or chloride, with a compound H_2N-R_3, for example aniline, preferably in the presence of a base, for example sodium carbonate/ethanol or triethylamine/toluene.

Process (b): The ring closure to form the corresponding 4-amino-pyrrolo[2,3-d]pyrimidine is carried out, for example, in the presence of suitable bases, for example sodium ethanolate/-ethanol, preferably at elevated temperature, for example at 80°C [see, for example, E.C. Taylor *et al.*, *J. Amer. Chem. Soc.* **87** (1965) 1995-2003].

The amidine compounds of formula III can be prepared, for example, from the corresponding amino compounds of formula II in accordance with known methods of amidine synthesis, for example by reaction first with triethyl orthoformate, preferably at elevated temperature, and then with ammonia, preferably at room temperature.

Process (c): Suitable leaving groups are, for example, methanesulfonates or p-toluenesulfonates of hydroxy compounds of the formula R_3-OH, and halogen. Compounds of formula IV are preferably prepared using the methods of synthesis described for compounds of formula I, in which case R_3 is hydrogen. The reaction of compounds of formula IV with compounds of formula V is carried out in a manner known *per se*. For example, a methanesulfonate of formula V is reacted with a pyrrolo[2,3-d]pyrimidine of formula IV in the presence of a base, for example potassium carbonate. The reaction is preferably carried out at elevated temperature, for example at from 50°C to the reflux temperature of the reaction mixture, especially at from 60 to 80°C, and advantageously in an inert solvent or solvent mixture. The reaction can be accelerated in an advantageous manner by the addition of a suitable crown ether. In a further process, the reaction takes place in a manner known *per se* under the conditions of phase transfer catalysis (E.V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, Weinheim, 1993). The reactants of formulae IV and V are dissolved in a suitable inert solvent or solvent mixture, and the second phase is formed by a concentrated aqueous alkali metal hydroxide solution, for example 30% sodium hydroxide solution. Advantageously, a phase transfer catalyst, for example a quaternary ammonium halide, such as tetrabutylammonium bromide, is added.

Process (d): The reaction of a compound of formula IV with a compound that can be converted into a radical R_3 is carried out in a manner known *per se*. It is advantageously carried out in an inert solvent or solvent mixture with cooling, at ambient temperature or at elevated temperature up to the reflux temperature of the reaction mixture, especially with ice-cooling, at room temperature or at elevated temperature up to the reflux temperature. The reaction can take place without the addition of a catalyst or auxiliary reagent, as in the case of, for

example, a cycloalk-1-en-3-one, or with such an addition; for example the reaction with a cycloalkane epoxide can advantageously be carried out with the addition of an alkali metal hydride, for example lithium hydride, and the reaction with a cycloalkene or cycloalkene epoxide in the presence of a tetra(triarylphosphine)palladium(0) compound, for example tetra(triphenylphosphine)palladium(0).

Compounds of formula I can be converted into other compounds of formula I. For example, in a manner known *per se* substituents in the aryl radical R_1 can be converted into one another.

For example, halo-lower alkyl, e.g. chloromethyl, can be reacted, for example, with unsubstituted or substituted lower alkanols, lower alkanethiols or lower alkylamines in accordance with a nucleophilic substitution reaction, yielding unsubstituted or substituted lower alkoxy-lower alkyl, lower alkylthio-lower alkyl or lower alkylamino-lower alkyl, respectively.

Hydroxy can be converted, for example, with unsubstituted or substituted halo-lower alkanes, yielding unsubstituted or substituted lower alkoxy. Hydroxy can, for example, also be reacted initially with a di-halo-lower alkane, for example 1-bromo-2-chloroethane, ω-halo-lower alkoxy being obtained; the latter can be reacted in a manner analogous to that described above with unsubstituted or substititued lower alkanols, lower alkanethiols or lower alkylamines in accordance with a nucleophilic substitution reaction, yielding unsubstituted or substituted lower alkoxy-lower alkoxy, lower alkylthio-lower alkoxy or lower alkylamino-lower alkoxy, respectively.

Analogously to hydroxy, mercapto can also be alkylated as described in the preceding paragraph.

Lower alkylthio groups can be converted by targeted oxidation both into lower alkylsulfinyl groups and into lower alkylsulfonyl groups.

Amino groups and hydroxy groups can be acylated in known manner, yielding, for example, lower alkanoylamino or lower alkanoyloxy groups, respectively.

Carboxylic acid radicals can be converted in accordance with known derivatisation methods, such as esterification or amide formation, into carboxylic acid derivatives, such as lower alkoxycarbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N,N-di-lower alkylamino-carbonyl, cyano or amidino. Conversely, carboxylic acid derivatives can also be converted into free carboxylic acids, for example by hydrolysis.

Compounds of formula I wherein R_2 is hydrogen can be converted by reaction with a halogenating agent, for example a N-halosuccinimide, into compounds of formula I wherein R_2 is halogen.

Substituents in the radical R_3 can be converted in a manner known *per se* into other substituents.

For example, hydroxy groups can be esterified with organic or inorganic acids or etherified with alcohols or organic halides or they can be removed by reduction.

Carbonyl groups can be converted by means of catalytic hydrogenation into methylene groups, or with diols or aminols into heterocyclic spiro-linked radicals.

If any of the intermediates contain interfering reactive groups, for example carboxy, hydroxy, mercapto or amino groups, those groups can be protected temporarily by readily removable protecting groups. The choice of suitable protecting groups, their introduction and their removal are known *per se* and are described, for example, in J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, London, New York 1973.

Salts of compounds I can be prepared in a manner known *per se*. For example, acid addition salts of compounds I are obtained by treatment with a suitable acid or a suitable ion exchange reagent and salts with bases by treatment with a suitable base or a suitable ion exchange reagent. Salts of compounds of formula I can be converted into the free compounds I in customary manner; acid addition salts, for example, by treatment with a suitable basic agent or a suitable ion exchange reagent and salts with bases, for example, by treatment with a suitable acid or a suitable ion exchange reagent.

Salts of compounds I can be converted in a manner known *per se* into other salts of compounds I; acid addition salts can be converted, for example, into other acid addition salts, for example by treatment of a salt of an inorganic acid, such as a hydrochloride, with a suitable metal salt, such as a sodium, barium or silver salt, of an acid, for example with silver acetate, in a suitable solvent in which an inorganic salt that forms, for example silver chloride, is insoluble and thus precipitates from the reaction mixture.

Depending upon the procedure and reaction conditions, compounds I having salt-forming properties can be obtained in free form or in the form of salts.

Owing to the close relationship between the compound I in free form and in the form of its salts, hereinabove and hereinbelow any reference to the free compound I or its salts should be understood as including also the corresponding salts or the free compound I, respectively, as appropriate and expedient.

The compounds I, including the salts of salt-forming compounds, can also be obtained in the form of their hydrates and/or may include other solvents, for example solvents that may have been used for the crystallisation of compounds in solid form.

Depending upon the starting materials and procedures chosen, the compounds I and their salts may be in the form of one of the possible isomers or in the form of a mixture thereof. There are obtainable as pure isomers, for example, pure diastereoisomers. Accordingly, mixtures of isomers may be in the form of, for example, mixtures of diastereoisomers. Isomeric mixtures of compounds I in free form or in salt form obtainable in accordance with the process or by another method can be separated into their components in customary manner, for example on the basis of the physico-chemical differences between the constituents in known manner by fractional crystallisation, distillation and/or chromatography. Advantageously, the more active isomer is isolated.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a derivative or salt or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials and intermediates, in each case in free form or in salt form, which result in the compounds I described at the beginning as being especially valuable or the salts thereof. The invention relates also to novel starting materials and intermediates, in each case in free form or in salt form, for the preparation of compounds I or the salts thereof, to the use thereof and to processes for their preparation, the variable R being as defined for compounds I.

The invention relates also to the use of compounds I and their pharmaceutically acceptable salts in the treatment of allergic conditions and diseases, preferably in the form of pharmaceutically acceptable preparations, especially in a method for the therapeutic treatment of the animal or human body, and to such a method of treatment.

The invention relates also to pharmaceutical compositions comprising as active ingredient a compound I or a pharmaceutically acceptable salt thereof, and to processes for their preparation. Those pharmaceutical compositions are, for example, for enteral, such as especially oral, also rectal, administration, for parenteral administration and for local administration to warm-blooded animals, especially humans, the compositions comprising the pharmacological active ingredient on its own or together with customary pharmaceutical excipients. The pharmaceutical compositions comprise (in percent by weight) for example from approximately 0.001% to 100%, preferably from approximately 0.1% to approximately 50%, active ingredient.

Pharmaceutical compositions for enteral or parenteral administration are, for example, those in unit dose forms, such as dragées, tablets, capsules or suppositories, and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising procedures. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary after the addition of appropriate excipients, into tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also have been added.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base material. Suitable suppository base materials are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules which comprise a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

Pharmaceutical compositions for local administration are, for example for topical treatment of the skin, lotions, creams and ointments, i.e. liquid or semi-solid oil-in-water or water-in-oil emulsions, fatty ointments, which are anhydrous, pastes, i.e. creams and ointments having secretion-absorbing powder constituents, gels, which are aqueous, of low water content or anhydrous and consist of swellable, gel-forming materials, foams, i.e. liquid oil-in-water emulsions in aerosol form which are administered from pressurised containers, and tinctures having an aqueous-ethanolic base and may comprise other customary pharmaceutical excipients, such as preservatives. The pharmaceutical compositions for local administration are prepared in a manner known *per se* by mixing the active ingredient with the pharmaceutical excipients, for example by dissolving or suspending the active ingredient in the base or in a portion thereof, if necessary. In order to prepare emulsions in which the active ingredient is dissolved in one of the liquid phases, the active ingredient is generally dissolved therein prior to emulsification; in order to prepare suspensions in which the active ingredient is suspended in the emulsion, the active ingredient is mixed with a portion of the base after emulsification and then added to the remainder of the formulation.

The dosage of the active ingredient can depend upon various factors, such as the effectiveness and duration of action of the active ingredient, the severity of the disease to be treated and of its symptoms, the mode of administration, the species of warm-blooded animal, and the sex, age, weight and/or individual condition of the warm-blooded animal. In a normal case, the, for example oral, daily dose for a warm-blooded animal weighing approximately 75 kg is estimated to be from approximately 1 mg to approximately 1000 mg, especially from approximately 5 mg to approximately 200 mg. It can be administered, for example, as a single dose or in several part doses of, for example, from 10 to 100 mg.

The following Examples are intended to illustrate the invention described hereinbefore, but without limiting the invention thereto. (Hereinbefore and hereinafter, unless otherwise indicated the meanings of the following abbreviations are: M.p.: = melting point; DMSO-d_6 = hexadeuterodimethyl sulfoxide).

Example 1: 5-Phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

a) N-(2-Oxo-2-phenyl-ethyl)-acetamide: 25.0 g of phenacylamine hydrochloride are suspended in a mixture of 150 ml of tetrahydrofuran, 40.5 ml of triethylamine and 27.6 ml of acetic anhydride. The suspension is stirred for 2.5 hours at room temperature and then filtered and the solvent is removed using a rotary evaporator. The residue is crystallised from diethyl ether. M.p.: 95-96°C.

b) 2-Amino-4-phenyl-1H-pyrrole-3-carbonitrile: 0.9 g of sodium is dissolved in 100 ml of ethanol, and 2.6 g of malonic acid dinitrile are added. The reaction mixture is stirred for 30 minutes at 55°C and then 7.0 g of N-(2-oxo-2-phenyl-ethyl)-acetamide are added thereto. The reaction mixture is then stirred for 2 hours at 55°C and poured onto ice and the product is filtered. ^{1}H-NMR (DMSO-d_6, ppm): 10.4 (s, 1H), 7.6-7.1 (m, 5H), 6.62 (s, 1H), 5.75 (s, 2H).

c) N-[3-Cyano-4-(4-methoxy-phenyl)-1H-pyrrol-2-yl]-formamidine: 6.0 g of 2-amino-4-phenyl-1H-pyrrole-3-carbonitrile are dissolved in 80 ml of triethyl orthoformate and the solution is stirred for 1 hour at 140°C. Triethyl orthofomate is removed under a high vacuum and the residue is dissolved in saturated methanolic ammonia. The solution is stirred for 24 hours at room temperature and then filtered. The product is recrystallised from ethanol. M.p.: 238-239°C.

d) 5-Phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine: 4.3 g of N-[3-cyano-4-(4-methoxy-phenyl)-1H-pyrrol-2-yl]-formamidine are suspended in 150 ml of ethanol, and 0.3 g of sodium ethanolate is added thereto. The reaction mixture is stirred for 1 hour under reflux and then cooled to room temperature and the product is filtered off. M.p.: 260-261°C.

Example 2: 5-(3-Methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

a) 2-Bromo-1-(3-methoxy-phenyl)-ethanone: A mixture of 10 ml of diethyl ether and 10 ml of 3-methoxy-acetophenone is cooled to 5°C, then 0.2 g of aluminium chloride is added and the reaction mixture is stirred for 5 minutes at 5°C. Then 3.9 ml of bromine are added drop-wise at 0-5°C and the mixture is then stirred for a further one hour at 0-5°C. The reaction mixture is poured into ethyl acetate and washed with water, saturated aqueous ammonium chloride and saturated sodium chloride solution. The organic layer is dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is crystallised from ether/petroleum ether. M.p.: 64-65°C.

b) 2-Azido-1-(3-methoxy-phenyl)-ethanone: 12.0 g of 2-bromo-1-(4-methoxy-phenyl)-ethanone and 1.0 g of tricaprylmethylammonium chloride (aliquot 366) are introduced into 300 ml of toluene, and a solution of 13.6 g of sodium azide in 40 ml of water is added drop-wise thereto. The reaction mixture is stirred for 1.5 hours at 50-55°C and then cooled to room temperature. The aqueous layer is separated off and extracted with toluene. The organic layers are combined, washed with water and dried and the solvent is removed using a rotary evaporator. Flash chromatography with diethyl ether/petroleum ether as eluant yields the product in the form of an oil, ^{1}H-NMR ($CDCl_3$, ppm): 7.5-7.1 (m, 4H), 4.55 (s, 2H), 3.9 (s, 3H).

c) 2-Amino-1-(3-methoxy-phenyl)ethanone hydrochloride: 7.7 g of 2-azido-1-(4-methoxy-phenyl)-ethanone are dissolved in a mixture of 150 ml of methanol and 12 ml of 4N hydrochloric acid and hydrogenated over 1.5 g of palladium-on-carbon (10%) for one hour with hydrogen under normal pressure. The hydrogenation solution is filtered and the filtrate is concentrated by evaporation. ^{1}H-NMR (DMSO-d_6, ppm): 8.5 (s (broad), 2H), 7.6-7.3 (m, 4H), 4.5 (q, 2H), 3.8 (s, 3H).

d) N-2-[2-(3-Methoxy-phenyl)-2-oxo-ethyl]acetamide: 7.60 g of 2-amino-1-(3-methoxy-phenyl)-ethanone hydrochloride are suspended in a mixture of 60 ml of tetrahydrofuran, 10.5 ml of triethylamine and 7.1 ml of acetic anhydride and the suspension is stirred for 2 hours at room temperature. The suspension is filtered and the filtrate is concentrated by evaporation. The residue is taken up in ethyl acetate and washed with water. The organic

layer is dried over sodium sulfate and the solvent is removed using a rotary evaporator, yielding a crystalline residue which is stirred with ether. M.p.: 109-110°C.

e) 2-Amino-4-(3-methoxy-phenyl)-1H-pyrrole-3-carbonitrile: 2.03 g of malonic acid dinitrile are added to a solution of 0.71 g of sodium in 100 ml of ethanol. The reaction mixture is stirred for 30 minutes at 55°C and then 6.38 g of N-2-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-acetamide are added thereto. The reaction mixture is stirred for a further 2 hours at 55°C and then poured onto ice and the product is filtered off. M.p.: 117-119°C.

f) N-[3-Cyano-4-(3-methoxy-phenyl)-1H-pyrrol-2-yl]-formamidine: N-[3-Cyano-4-(3-methoxy-phenyl)-1H-pyrrol-2-yl]-formamidine is dissolved in 50 ml of triethyl orthoformate and the solution is stirred for 1 hour at 140°C. Excess triethyl orthoformate is removed under a high vacuum and the residue is dissolved with saturated methanolic ammonia solution. The resulting solution is stirred for 20 hours at room temperature and then filtered. The product is recrystallised from ethanol. M.p.: 188-190°C.

g) 5-(3-Methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine: 0.43 g of sodium ethanolate is dissolved in 100 ml of ethanol, and 5.0 g of N-[3-cyano-4-(3-methoxy-phenyl)-1H-pyrrol-2-yl]-formamidine are added thereto. The reaction mixture is stirred for 1 hour under reflux and on cooling to room temperature the product precipitates and is filtered. M.p.: 249-250°C.

Example 3: 5-(4-Benzyloxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

a) 1-[4-(Benzyloxy)phenyl]ethanone: 48 ml of benzyl bromide are added dropwise to a suspension of 50.0 g of 4-hydroxyacetophenone and 76.0 g of potassium carbonate in 600 ml of acetone. The reaction mixture is stirred for 20 hours under reflux and then filtered. The filtrate is concentrated by evaporation and the residue is triturated with petroleum ether. ^{1}H-NMR ($CDCl_3$, ppm): 7.55 (m, 2H), 7.46 (m, 6H), 7.17 (ddd, 1H), 5.11 (s, 2H), 2.57 (s, 3

b) 2-Bromo-1-(4-benzyloxy-phenyl)-ethanone: 173 g of copper(II) bromide are suspended in 580 ml of ethyl acetate and the suspension is heated at reflux temperature. Then a solution of 1-[3-(benzyloxy)phenyl]ethanone in 330 ml of chloroform is added dropwise in the course of 40 minutes. After stirring for 2 hours under reflux, the suspension is cooled to room tem-

perature and filtered. The filtrate is concentrated by evaporation and the product is purified by flash chromatography (dichloromethane/petroleum ether 1:1). M.p.: 58-59°C.

c) 2-Amino-1-(4-benzyloxy-phenyl)ethanone hydrochloride: 50.0 g of 2-bromo-1-(4-benzyl-oxy-phenyl)-ethanone are dissolved in 1 litre of chloroform, and 35 g of hexamethylene tetramine are added thereto. The reaction mixture is stirred for 20 hours at room temperature. The product is filtered off, dissolved in 300 ml of ethanol/100 ml of concentrated hydrochloric acid and boiled for 2 hours under reflux. The reaction mixture is cooled to room temperature and the product is filtered off. M.p.: 237-240°C (decomposition).

d) N-2-[2-(4-Benzyloxy-phenyl)-2-oxo-ethyl]-acetamide: 28.2 g of 2-amino-1-(4-benzyloxy-phenyl)-ethanone hydrochloride are suspended in 300 ml of tetrahydrofuran, and 28.2 ml of triethylamine and 11.5 ml of acetic anhydride are added thereto. The reaction mixture is stirred for 3 hours at room temperature and filtered and the mother liquor is concentrated by evaporation using a rotary evaporator. The residue is taken up in diethyl ether and the product is precipitated with petroleum ether, ^{1}H-NMR ($CDCl_3$, ppm): 7.8 (d, 2H), 7.4 (m, 5H), 7.02 (d, 2H), 6.6 (t, 1H), 5.18 (s, 2H), 4.7 (d, 2H), 2.1 (s, 3H).

e) 2-Amino-4-(4-benzyloxy-phenyl)-1H-pyrrole-3-carbonitrile: 4.5 g of malonic acid dinitrile are added to a solution of 1.5 g of sodium in 300 ml of ethanol. The reaction mixture is stirred for 30 minutes at 40°C and then 16.1 g of N-2-[2-(4-benzyloxy-phenyl)-2-oxo-ethyl]-acetamide are added. The reaction mixture is stirred for 18 hours at 40°C and then cooled to room temperature and the product is filtered off. ^{1}H-NMR (DMSO-d_6, ppm): 10.3 (s, 1H), 7.48 (d, 2H), 7.35 (m, 5H), 7.0 (d, 2H), 6.4 (s, 1H), 5.7 (s, 2H), 5.1 (s, 2H).

f) 5-(4-Benzyloxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine: 15.2 g of 2-amino-4-(4-benzyloxy-phenyl)-1H-pyrrole-3-carbonitrile are dissolved in 200 ml of triethyl orthoformate and the solution is stirred for 1 hour at 140°C. Triethyl orthoformate is concentrated by evaporation under a high vacuum and the residue is dissolved in 500 ml of saturated methanolic ammonia solution. After stirring for 20 hours at room temperature, the suspension is filtered and the violet crystals are washed thoroughly with methanol. M.p.: 220°C (decomposition).

Analogously to the above Examples, starting in each case from suitably substituted acetophenone derivatives the corresponding pyrrolopyrimidines are prepared:

Example 4: 5-(4-Methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine, m.p.: 278-281°C

Example 5: 5-(3-Benzyloxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine, m.p.: 241-243°C

Example 6: 5-(3-Fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 7: 5-(4-Fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 8: 5-(3-Chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 9: 5-(4-Chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 10: 5-(3-Bromo-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 11: 5-(4-Bromo-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 12: 5-*p*-Tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 13: 5-*m*-Tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 14: 5-(4-Trifluoromethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 15: 5-(3-Trifluoromethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine

Example 16: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopent-2-en-ol
0.25 g of tetrakis(triphenylphosphine)palladium(0) and 1.09 g of 5-phenyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl-amine (Example 1) are dissolved in 12 ml of tetrahydrofuran/dimethyl sulfoxide (1:1) and the reaction mixture is stirred for 2 minutes at room temperature and then cooled to 0°C. A solution of 0.4 g of cyclopentadiene monoepoxide in 8 ml of tetrahydrofuran is then slowly added dropwise thereto at 0°C. The reaction mixture is stirred for 3 hours

at 0°C and for 16 hours at room temperature. The reaction mixture is then poured into dichloromethane and washed with saturated aqueous ammonium chloride. The organic layer is dried and the solvent is removed using a rotary evaporator. The residue is purified by flash chromatography (dichloromethane/methanol, 95:5). ^{1}H-NMR (DMSO-d_6, ppm): 8.18 (s, 1H), 7.48-7.31 (m, 5H), 7.25 (s, 1H), 6.2 (s, 2H), 6.15 (m, 1H), 5.95 (m, 1H), 5.72 (m, 1H), 5.32 (d, 1H), 4.7 (m, 1H), 2.9 (m, 1H), 1.62 (m, 1H).

Cyclopentadiene monoepoxide *[CAS Reg. No.: 7129-41-1]* is prepared according to V. Merlo *et al., J. Chem. Soc. Perkin Transaction I* **1994**, 1477.

The following are prepared analogously to Example 16:

Example 17: 4-[4-Amino-5-(4-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopent-2-en-ol

Example 18: 4-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopent-2-en-ol

Example 19: 4-(4-Amino-5-(4-benzyloxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopent-2-en-ol
Prepared analogously to Example 1, starting from 5-(4-benzyloxy-phenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-yl-amine (Example 3) and cyclopentadiene monoepoxide. ^{1}H-NMR (CD_3OD, ppm): 8.1 (s, 1H), 7.32 (m, 7H), 7.1 (s, 1H), 7.0 (d, 2H), 6.18 (m, 1H), 5.9 (m, 1H), 5.75 (m, 1H), 5.05 (s, 2H), 4.7 (m, 1H), 2.95 (m, 1H), 1.75 (m, 1H).

Example 20: 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopentanol
A solution of 4-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopent-2-en-ol (Example 16) in 15 ml of dimethylformamide is hydrogenated over 30 mg of palladium-on-carbon (10%) under normal pressure with hydrogen. The catalyst is filtered off and the filtrate is taken up in ethyl acetate. The organic layer is extracted three times with water and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The residue is triturated with ether. ^{1}H-NMR (DMSO-d_6, ppm): 8.18 (s, 1H), 7.51-7.3 (m, 6H), 6.1 (s (broad), 2H), 5.2 (m, 1H), 5.05 (d, 1H), 4.28 (m, 1H), 2.42 (m, 2H), 2.1 (m, 2H), 1.7 (m, 2H).

3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopentanol is also obtained by a route analogous to that described in Example 44, starting from 3-(4-amino-5-phenyl-pyrrolo-[2,3-d]pyrimidin-7-yl)-cyclopentanone.

The following are prepared analogously to Example 20:

Example 21: 3-[4-Amino-5-(4-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopentanol

Example 22: 3-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopentanol

Example 23: 3-(4-Amino-5-(4-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopentanol
50 mg of palladium-on-carbon (10%) are added to a solution of 0.2 g of 4-(4-amino-5-(4-benzyloxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopent-2-en-ol (Example 19) in 12 ml of methanol and the reaction mixture is hydrogenated with hydrogen analogously to Example 3. The catalyst is filtered off and methanol is removed using a rotary evaporator. The residue is triturated with ether. ^{1}H-NMR (DMSO-d_6, ppm): 9.5 (s, 1H), 8.1 (s, 1H), 7.32 (s, 1H), 7.22 (d, 2H), 6.85 (d, 2H), 6.0 (s (broad), 2H), 5.15 (m, 1H), 5.05 (d, 1H), 4.23 (m, 1H), 2.4 (m, 2H), 2.08 (m, 2H), 1.75 (m, 2H).

Alternatively, the synthesis of the cyclopentenol derivatives can also be carried out starting from 3-acetoxy-5-hydroxycyclopent-1-ene (*cis*-3-acetoxy-5-hydroxycyclopent-1-ene: *[CAS Reg. No.: 60410-18-6]* and *trans*-3-acetoxy-5-hydroxycyclopent-1-ene: *[CAS Reg. No.: 60410-15-3]*). The hydroxy group of the corresponding 3-acetoxy-5-hydroxycyclopent-1-ene is p-toluenesulfonated or methanesulfonated, followed by alkylation with the desired 5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine.

There is prepared analogously to Example 23:

Example 24: 3-(4-Amino-5-(3-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopentanol

Example 25: 5-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-3-benzyloxy-2-benzyloxy-methyl-cyclopentanol

A solution of 0.75 g of 5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine (Example 1) and 0.025 g of lithium hydride in 12 ml of dimethylformamide is stirred for 1 hour at 120°C. The reaction mixture is then cooled to room temperature and 0.930 g of 3-benzyloxy-2-benzyl-oxymethyl-6-oxa-bicyclo[3.1.0]hexane 1s-(1α2α3β5α) is added thereto. The reaction mixture is then heated for 3.5 hours with stirring at 145°C. The reaction mixture is taken up in ethyl acetate and the organic layer is extracted three times with water. The organic layer is dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is purified by flash chromatography (dichloromethane/methanol 10:0.3). ^{1}H-NMR ($CDCl_3$, ppm): 8.22 (s, 1H), 7.4 (m, 15H), 6.9 (s, 1H), 5.2 (s, 2H), 4.9 (m, 1H), 4.53 (m, 4H), 4,3 (t, 1H), 4.05 (m, 1H), 3.65 (m, 2H), 2.55 (m, 2H), 2.35 (m, 1H).

3-Benzyloxy-2-benzyloxymethyl-6-oxa-bicyclo[3.1.0]hexane 1s-(1α2α3β5α) *[CAS Reg. No.: 110567-22-1]* is prepared analogously to K. Biggadike *et al. J. Chem. Soc. Chem. Commun.* **1987**, 255.

Example 26: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxymethyl-cyclo-pentane-1,3-diol

0.1 ml of 4N hydrochloric acid and 40 mg of palladium-on-carbon (10%) are added to a solution of 0.130 g of 5-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-3-benzyloxy-2-benzyloxymethyl-cyclopentanol (Example 25) in 10 ml of methanol/ethyl acetate (1:1) and the reaction mixture is hydrogenated with hydrogen under normal pressure. The catalyst is filtered off and the filtrate is concentrated using a rotary evaporator. The product is purified by flash chromatography with dichloromethane/methanol (10:1.5) as eluant. ^{1}H-NMR (DMSO-d_6, ppm): 8.12 (s, 1H), 7.52-7.30 (m, 6H), 5.02 (m, 1H), 4.10 (m, 2H), 3.55 (m, 2H), 2.12 (m, 1H), 2.00 (m, 1H), 1.80 (m, 1H).

The following are prepared analogously:

Example 27: 4-[4-Amino-5-(4-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxy-methyl-cyclopentane-1,3-diol

Example 28: 4-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxy-methyl-cyclopentane-1,3-diol

Example 29: 4-[4-Amino-5-(4-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxymethyl-cyclopentane-1,3-diol

Example 30: 4-[4-Amino-5-(3-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxymethyl-cyclopentane-1,3-diol

Example 31: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxymethyl-cyclo-pentanol

a) [7-(4-Benzyloxy-3-benzyloxymethyl-2-(tert-butyl-dimethyl-silanyloxy)-cyclopentyl]-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine: 0.250 g of 5-(4-amino-5-phenyl-pyrrolo-[2,3-d]pyrimidin-7-yl)-3-benzyloxy-2-benzyloxymethyl-cyclopentanol (Example 26), 0.270 g of tert-butyldimethylsilyl chloride and 0.125 g of imidazole are dissolved in 8 ml of dichloromethane and the reaction mixture is stirred for 10 hours at room temperature. The reaction mixture is taken up in dichloromethane and washed with saturated aqueous ammonium chloride and water. The organic layer is separated off and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is purified by flash chromatography (dichloromethane). ^{1}H-NMR ($CDCl_3$, ppm): 8.31 (s, 1H), 7.4 (m, 15H), 7.0 (s, 1H), 5.2 (s, 2H), 5.1 (m, 1H), 4.53 (m, 5H), 4.15 (m, 1H), 3.65 (m, 2H), 2.50 (m, 1H), 2.30 (m, 3H), 0.7 (s, 6H), 0.0 (s, 9H).

b) [7-[4-Benzyloxy-3-benzyloxymethyl-2-(tert-butyl-dimethyl-silanyloxy)-cyclopentyl]-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-carbamic acid benzyl ester: 0.405 g of benzyloxy-carbonyl-imidazolide is dissolved in 18 ml of dichloromethane and the solution is cooled to 0°C. Then 0.380 g of triethyloxonium tetrafluoroborate is added and the reaction mixture is stirred for 3 hours at room temperature. Then 0.140 g of [7-(4-benzyloxy-3-benzyloxy-methyl-2-(tert-butyl-dimethyl-silanyloxy)-cyclopentyl]-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine is added and the mixture is stirred for a further 24 hours at room temperature. The reaction mixture is taken up in dichloromethane and washed with aqueous ammonium chloride (saturated) and water. The organic layer is separated off and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is purified by flash chro-

matography (diethyl ether/hexane 8:2). ^{1}H-NMR ($CDCl_3$, ppm): 8.72 (s, 1H), 7.4 (m, 20H), 7.13 (s, 1H), 5.8 (s, 1H), 5.15 (m, 1H), 5.1 (s, 2H), 4.7 (m, 1H), 4.50 (m, 4H), 4.15 (m, 1H), 3.75 (m, 2H), 2.55 (m, 1H), 2.30 (m, 3H), 0.7 (s, 6H), 0.0 (s, 9H).

c) [7-(4-Benzyloxy-3-benzyloxymethyl-2-hydroxy-cyclopentyl)-5-phenyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl]-carbamic acid benzyl ester: 0.150 g of {7-[4-benzyloxy-3-benzyloxymethyl-2-(tert-butyl-dimethyl-silanyloxy)-cyclopentyl]-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl}-carbamic acid benzyl ester is dissolved in 4 ml of tetrahydrofuran/dimethylformamide (1:1), and 0.030 g of tetrabutylammonium fluoride is added thereto. The reaction mixture is stirred for 4 hours at 40°C and for 18 hours at room temperature, taken up in ethyl acetate and extracted with water. The organic layer is separated off and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is purified by flash chromatography (dichloromethane/methanol 10:0.3). ^{1}H-NMR ($CDCl_3$, ppm) 8.72 (s, 1H), 7.4 (m, 20H), 7.13 (s, 1H), 5.8 (s, 1H), 5.1 (s, 2H), 4.9 (m, 1H), 4.53 (m, 4H), 4.3 (t, 1H), 4.05 (m, 1H), 3.65 (m, 2H), 2.55 (m, 2H), 2.35 (m, 1H).

d) Thiocarboxylic acid O-[3-benzyloxy-5-(4-benzyloxycarbonylamino-5-phenyl-pyrrolo[2,3-d]-pyrimidin-7-yl)-2-benzyloxymethyl-cyclopentyl]-ester O-phenyl ester: 0.040 g of [7-(4-benzyloxy-3-benzyloxymethyl-2-hydroxy-cyclopentyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-carbamic acid benzyl ester is dissolved in 1 ml of pyridine/dichloromethane (1:1) and cooled to 0°C. 0.014 ml of chlorothioformic acid O-phenyl ester is added and the solution is stirred for 2 hours at 0°C and for 3 hours at room temperature. The reaction mixture is taken up in dichloromethane and washed with saturated aqueous ammonium chloride and water. The organic layer is separated off and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The product is purified by flash chromatography (diethyl ether/ hexane 1:2). ^{1}H-NMR ($CDCl_3$, ppm): 8.72 (s, 1H), 7.6-6.8 (m, 26H), 6.2 (t, 1H), 5.8 (s, 1H), 5.15 (m, 1H), 5.10 (s, 2H), 4.7 (m, 4H), 4.6 (m, 1H), 4.15 (m, 1H), 3.80 (m, 2H), 2.60 (m, 1H), 2.50 (m, 1H).

e) 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxymethyl-cyclopentanol: 5 mg of aza-isobutyronitrile are added to a solution of 0.050 g of thiocarboxylic acid O-[3-benzyloxy-5-(4-benzyloxycarbonylamino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-2-benzyloxymethyl-cyclopentyl]-ester O-phenyl ester and 0.03 ml of tributyltin hydride in 3 ml of toluene. The

reaction mixture is stirred for 3 hours at 75°C and then taken up in ethyl acetate and extracted with aqueous ammonium chloride and water. The organic layer is separated off and dried over sodium sulfate and the solvent is removed using a rotary evaporator. The residue is partitioned between acetonitrile and hexane and the acetonitrile layer is extracted twice with hexane. The acetonitrile layer is concentrated by evaporation using a rotary evaporator and the residue is dried under a high vacuum. Without being purified further, the crude product is dissolved in 5 ml of methanol, and 4 drops of 4N hydrochloric acid and 0.010 g of palladium-on-carbon (10%) are added thereto. Hydrogenation is carried out under normal pressure with hydrogen, the catalyst is filtered off and the filtrate is concentrated. The product is purified by flash chromatography with dichloromethane/methanol (10:1) as eluant. ^{1}H-NMR (CD_3OD, ppm): 8.1 (s, 1H), 7.52-7.32 (m, 5H), 7.30 (s, 1H), 5.4 (m, 1H), 4.22 (m, 1H), 3.7 (m, 2H), 2.45 (m, 1H), 2.32 (m, 1H), 2.2 (m, 1H), 1.8 (m, 1H), 1.6 (m, 1H), 1.4 (m, 1H).

The following are prepared analogously:

Example 32: 4-[4-Amino-5-(4-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxymethyl-cyclopentanol

Example 33: 4-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxymethyl-cyclopentanol

Example 34: 4-[4-Amino-7-(3-hydroxy-4-hydroxymethyl-cyclopentyl)-7H-pyrrolo[2,3-d]-pyrimidin-5-yl]-phenol

Example 35: 3-[4-Amino-7-(3-hydroxy-4-hydroxymethyl-cyclopentyl)-7H-pyrrolo[2,3-d]-pyrimidin-5-yl]-phenol

Example 36: 4-Amino-7-cyclopentyl-5-phenyl-pyrrolo[2,3-d]pyrimidine

(a) 2-Cyclopentylamino-acetophenone: A mixture of 2.0 g of cyclopentylamine, 4.67 g of phenacyl bromide and 7.46 g of powdered potassium carbonate is stirred in 40 ml of ethanol for 1 hour under argon at room temperature. Undissolved potassium carbonate is filtered off and washed with ether. The organic layer is washed with water and sodium chloride solution, dried over sodium sulfate and concentrated and yields an orange-brown oil

which solidifies on being left to stand. The product is used in the following step without being purified further.

(b) 2-Amino-3-cyano-1-cyclopentyl-4-phenylpyrrole: 0.60 g of sodium is dissolved in 50 ml of absolute ethanol. There are added dropwise thereto first 1.86 g of malonic acid dinitrile and then crude 2-cyclopentylamino-acetophenone, dissolved in 25 ml of ethanol. After heating for 6 hours at 50°C, the reaction mixture is poured onto ice and extracted with ethyl acetate. The crude product is purified by flash chromatography (ethyl acetate/hexane 1:3). ^{1}H-NMR ($CDCl_3$): 1.7-1.95 (m, 6H), 2.08-2.2 (m, 2H), 3.93 (br. m, 2H), 4.25-4.4 (m, 1H), 6.47 (s, 1H), 7.26 (t, 1H), 7.37 (t, 2H), 7.58 (d, 2H).

(c) 3-Cyano-1-cyclopentyl-4-phenyl-2-(N-aminoformimidato)-pyrrole: 1.92 g of crude 2-amino-3-cyano-1-cyclopentyl-4-phenylpyrrole and 0.2 ml of acetic anhydride in 20 ml of triethyl orthoformate are maintained at 80°C for 1 hour. The dark solution is concentrated and dried under a high vacuum. The residue is taken up in 20 ml of ammonia-saturated methanol and stirred for 60 hours at room temperature. The product is concentrated by evaporation and dried.

(d) 4-Amino-7-cyclopentyl-5-phenyl-pyrrolo[2,3-d]pyrimidine: A solution of 2.15 g of 3-cyano-1-cyclopentyl-4-phenyl-2-(N-aminoformimidato)-pyrrole in 100 ml of ethanol and 212 mg of sodium ethanolate is heated for 1 hour under reflux. After removal of the solvent, purification is carried out by flash chromatography (ethyl acetate/hexane 2:1). The product is obtained in the form of a brownish solid after crystallisation from diethyl ether/pentane. M.p.: 123-125°C. ^{1}H-NMR ($CDCl_3$): 1.7-2.0 (m, 6H), 2.2-2.35 (m, 2H), 5.12 (br. s, 2H), 5.15-5.3 (m, 1H), 7.04 (s, 1H), 7.33-7.55 (m, 5H), 8.46 (s, 1H).

The following are prepared analogously:

Example 37: 4-Amino-7-cyclohexyl-5-(4-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 38: 4-Amino-7-cyclohexyl-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 39: 4-Amino-7-cyclohexyl-5-(3-methoxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 40: 4-Amino-7-cyclopropyl-5-phenyl-pyrrolo[2,3-d]pyrimidine: m.p.: 140-141°C

Example 41: 4-Amino-7-cyclohexyl-5-phenyl-pyrrolo[2,3-d]pyrimidine: m.p.: 166-168°C

Example 42: 2-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)cyclohexanol: m.p.: 181-183°C

Example 43: 2-[3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexylamino]-ethanol

(a) 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclohexanone: A mixture of 2.10 g of 4-amino-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine and 5.0 ml of cyclohexenone in 50 ml of dimethylformamide is stirred for 5 hours at room temperature. After removal of most of the dimethylformamide, the residue is partitioned between ethyl acetate and water. The combined organic layers are washed three times with water and once with sodium chloride solution and dried over sodium sulfate. The crude product is purified by flash chromatography (ethyl acetate). After removal of the solvent, the title compound is obtained in the form of a reddish foam. ^{1}H-NMR ($CDCl_3$): 1.7-1.9 (m, 1H), 2.05-2.18 (m, 1H), 2.2-2.33 (m, 2H), 2.33-2.55 (m, 2H), 2.82-3.00 (m, 2H), 4.95-5.10 (m, 1H), 5.50 (br. s, 1H), 6.99 (s, 1H), 7.32-7.50 (m, 5H), 8.26 (s, 1H).

(b) 4-Amino-7-(1-oxa-4-aza-spiro[4,5]dec-7-yl)-5-phenyl-pyrrolo[2,3-d]pyrimidine: At room temperature, 60 µl of ethanolamine are added to a solution of 306 mg of 3-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclohexanone in 3 ml of absolute ethanol. After stirring for 16 hours the product (mixture of diastereoisomers) can be obtained by filtering the suspension.

(c) 2-[3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexylamino]-ethanol: 150 mg of crude 4-amino-7-(1-oxa-4-aza-spiro[4,5]dec-7-yl)-5-phenyl-pyrrolo[2,3-d]pyrimidine are dissolved in 10 ml of absolute methanol, and 20 mg of sodium borohydride are added thereto. After stirring for half an hour at 0°C, working-up is effected by diluting with water and extracting with ethyl acetate. Purification by means of preparative HPLC yields 3-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclohexan-1-one and the *cis-* and *trans-*forms of the diastereoisomeric title compound.

^{1}H-NMR (d_6-DMSO):

cis-diastereoisomer:

1.08-1.15 (m, 1H), 1.4-1.5 (m, 1H), 1.68 (q, 1H), 1.75-1.97 (m, 4H), 2.17 (d, 1H), 2.67 (t, 2H), 2.70-2.78 (m, 1H), 3.46 (t, 2H), 4.59-4.67 (m, 1H), 6.11 (broad, NH), 7.31-7.37 (m, 1H), 7.42-7.50 (m, 5H), 8.13 (s, 1H).

trans-diastereoisomer:

1.40-1.57 (m, 2H), 1.65-1.99 (m, 5H), 2.06 (td, 1H), 2.61 (t, 2H), 3.07 (br. s, 1H), 3.51 (t, 2H), 5.00-5.08 (m, 1H), 6.04 (broad, NH), 7.30-7.37 (m, 1H), 7.41-7.51 (m, 5H), 8.13 (d, 1H).

Example 44: 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexan-1-ol

A suspension of 211 mg of 3-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexanone and 20 mg of sodium borohydride in 5 ml of methanol is stirred for 1.5 hours at 5°C, then diluted with water and extracted with ethyl acetate. After drying over sodium sulfate and concentrating *in vacuo* the diastereoisomers are separated by means of preparative HPLC.

^{1}H-NMR ($CDCl_3$):

cis-diastereoisomer:

1.32-1.40 (m, 1H), 1.555 (qt, 1H), 1.69 (qd, 1H), 1.805 (dd, 1H), 1.97-2.03 (m, 1H), 2.08-2.16 (m, 2H), 2.41-2.46 (m, 1H), 3.89 (tt, 1H), 4.78 (tt, 1H), 5.85 (br, NH), 7.21 (s, 1H), 7.42-7.54 (m, 5H), 8.22 (s, 1H).

trans-diastereoisomer:

1.56-1.63 (m, 1H), 1.76-1.94 (m, 3H), 1.96-2.10 (m, 2H), 2.12-2.19 (m, 1H), 2.22-2.28 (m, 1H), 4.41 (br. s, 1H), 5.214 (tt, 1H), 5.79 (br. s, NH), 7.18 (s, 1H), 7.41-7.53 (m, 5H), 8.26 (s, 1H).

3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopentan-1-ol (Example 20) can also be prepared analogously.

Example 45: [4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopent-2-enyl]-methanol

A solution of 47 mg of allylpalladium chloride dimer and 136 mg of triphenylphosphine in 2 ml of tetrahydrofuran (distilled under argon over potassium) is stirred under argon for 1 hour at room temperature. There is added dropwise to the yellow suspension a solution of 272 mg of 4-amino-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine in 3 ml of dimethyl sulfoxide

(flushed with argon). After 15 minutes the reaction mixture is cooled to 0°C and 182 mg of (4aR*,7aR*)-4,4a,5,7a-tetrahydrocyclopenta[1,3]dioxin-2-one, dissolved in 3 ml of tetrahydrofuran (distilled under argon over potassium), are added dropwise thereto. After 2 hours at 0°C the reaction mixture is allowed to rise to room temperature and is stirred for 2 days at room temperature. The reaction solution is then partitioned between water and ethyl acetate and the aqueous layer is extracted twice with ethyl acetate. The organic layer is washed with saturated sodium chloride solution. Drying over magnesium sulfate and concentrating yield a yellow solid which is purified by flash column chromatography (dichloromethane/methanol 19:1). Pure [4-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopent-2-enyl]-methanol is obtained by means of preparative HPLC. ^{1}H-NMR ($CDCl_3$): 1.80 (td, 1H), 2.86 (td, 1H), 3.06-3.14 (m, 1H), 3.73 (dd, 1H), 3.83 (dd, 1H), 5.81 (br. s, 1H), 5.90 (dd, 1H), 6.00-6.05 (m, 1H), 6.19 (dd, 1H), 7.30 (s, 1H), 7.40-7.52 (m, 5H), 8.19 (s, 1H).

Example 46: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-(1,2,4/0)-cyclopentane-1,2-diol

(a) 7-(2,2-Dimethyl-tetrahydro-(1,2,4/0)-cyclopenta[1,3]dioxol-5-yl)-5-phenyl-7H-pyrrolo-[2,3-d]pyrimidin-4-yl-amine: A mixture of 187 mg of 4-amino-5-phenyl-7H-pyrrolo[2,3-d]-pyrimidine (Example 1), 245 mg of powdered potassium carbonate and 543 mg of 18-crown-6-ether in 2 ml of dimethylformamide is stirred for 15 minutes at 70°C. 252 mg of methanesulfonic acid [2,2-dimethyl-tetrahydro-(1,2/4)-cyclopenta[1,3]dioxol-5-yl] ester are added dropwise thereto. After stirring for 5 hours at 70°C, working-up is effected by partitioning between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated *in vacuo*. The crude product is purified by flash column chromatography (ethyl acetate/methanol 99:1). M.p.: 194-196°C.

Methanesulfonic acid [2,2-dimethyl-tetrahydro-(1,2/4)-cyclopenta[1,3]dioxol-5-yl] ester can be prepared by methanesulfonating 2,2-dimethyl-tetrahydro-(1,2/4)-cyclopenta[1,3]dioxol-5-ol (R. Steyn, H.Z. Sabble, *Tetrahedron* 25, 3579 (1969)).

(b) 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-(1,2,4/0)-cyclopentane-1,2-diol: 0.5 ml of 2N hydrochloric acid is added to a solution of 130 mg of 7-(2,2-dimethyl-tetrahydro-(1,2,4/0)-cyclopenta[1,3]dioxol-5-yl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine in 5 ml

of ethanol/water 95:5 and the reaction mixture is heated for 1 hour under reflux. After cooling to room temperature, the reaction mixture is poured into a mixture of water and ethyl acetate. The aqueous layer is rendered basic by the addition of saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. Drying over magnesium sulfate and concentrating yields the title compound, m.p.: 186-188 °C.

Example 47: {3-[4-Amino-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol

(a) 3-(4-Amino-5-(3-benzyloxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutanecarboxylic acid ethyl ester: A mixture of 1.08 g of 5-(3-benzyloxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine (Example 5), 0.95 g of powdered potassium carbonate and 1.81 g of 18-crown-6-ether in 15 ml of dimethylformamide is stirred for 20 minutes at 70°C. 1.00 g of 3-methanesulfonyloxy-cyclobutanecarboxylic acid methyl ester, dissolved in 5 ml of dimethylformamide, is added dropwise thereto. After stirring for 20 hours at 70°C, working-up is effected by partitioning between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated *in vacuo*. The crude product is purified by flash column chromatography (ethyl acetate/methanol 97:3). The product is obtained as an approx. 1:1 diastereoisomeric mixture in the form of a yellow oil.

3-Methanesulfonyloxy-cyclobutanecarboxylic acid methyl ester can be prepared by esterifying with methanol and subsequent methanesulfonating starting from 3-hydroxy-cyclobutanecarboxylic acid (see K. B. Wiberg *et al.*, *Tetrahedron* 21, 2763 (1965)).

(b) 3-[4-Amino-5-(3-benzyloxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol: A solution of 1.00 g of 3-(4-amino-5-(3-benzyloxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutanecarboxylic acid ethyl ester is added dropwise at 0°C to 96 mg of lithium aluminium hydride suspended in 10 ml of tetrahydrofuran. The reaction mixture is slowly warmed to room temperature overnight. For working-up, the reaction mixture is cooled to 0°C and then 42 µl of water, 42 µl of 15 percent sodium hydroxide solution and a further 218 µl of water are added in succession thereto. After half an hour the solid material is separated off and the filtrate is partitioned between water and ethyl acetate. Drying over magnesium sulfate, concentrating *in vacuo* and purifying by column chromatography (ethyl acetate/methanol

95:5) yield the pure diastereoisomers (*cis*/*trans*) in a ratio of approx. 3:4. M.p.: 138-140°C (*cis*-isomer), m.p.: 146-148°C (*trans*-isomer).

(c) cis-{3-[4-Amino-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol: 100 mg of *cis*-{3-[4-amino-5-(3-benzyloxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol are hydrogenated in 6 ml of methanol over 30 mg of palladium-on-carbon (10%). Purification by means of preparative HPLC yields the title compound. M.p.: 175-177°C.

(d) trans-{3-[4-Amino-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol: Analogously to (c), hydrogenation of *trans*-{3-[4-amino-5-(3-benzyloxyphenyl)-pyrrolo[2,3-d]-pyrimidin-7-yl]-cyclobutyl}-methanol yields the corresponding *trans*-diastereoisomer. M.p.: 228-230°C.

Example 48: 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclobutanol

(a) 7-(3-Benzyloxy-cyclobutyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine: A mixture of 317 mg of 4-amino-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine (Example 1), 417 mg of powdered potassium carbonate and 922 mg of 18-crown-6-ether (crystalline with one equivalent of acetonitrile) in 5 ml of dimethylformamide is stirred for 20 minutes at 70°C. 540 mg of methanesulfonic acid (3-benzyloxy)-cyclobutyl ester, dissolved in 5 ml of dimethylformamide, are added dropwise thereto. After stirring for 24 hours at 70°C, working-up is effected by partitioning between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated *in vacuo*. Purification of the crude product by flash column chromatography (dichloromethane/methanol 97:3) yields the product in the form of an approx. 1:1 diastereoisomeric mixture. M.p.: 146-148°C.

Methanesulfonic acid (3-benzyloxy)cyclobutyl ester can be prepared by reduction of 3-benzyloxy-cyclobutanone (see K. Ogura *et al. Bull. Chem. Soc. Jpn.* **57**, 1637 (1 4)) with lithium aluminium hydride and subsequent methanesulfonation.

(b) 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclobutanol: 235 mg of 7-(3-benzyloxy-cyclobutyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine are hydrogenated in 6 ml of methanol over 50 mg of palladium-on-carbon (10%). Separating off the catalyst, concen-

trating *in vacuo* and crystallising from ethyl acetate yield the title compound. M.p.: 196-199°C.

In analogous manner are prepared:

Example 49: *cis*-[3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclobutyl]-methanol, m.p.: 200-204°C

Example 50: *trans*-[3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclobutyl]-methanol, m.p.: 163-165°C

Example 51: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-(1,2/4)-cyclopentane-1,2-diol, m.p.: 189-191°C

Example 52: 4-Amino-7-cyclobutyl-5-phenyl-pyrrolo[2,3-d]pyrimidine, m.p.: 159-161°C

Example 53: 4-Amino-7-cyclopentyl-5-(4-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine, m.p.: 238-240°C

Example 54: 4-Amino-7-cyclopentyl-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 55: 4-Amino-7-cyclopentyl-5-(3-methoxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 56: 4-Amino-7-cyclopropyl-5-(4-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 57: 4-Amino-7-cyclopropyl-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 58: 4-Amino-7-cyclopropyl-5-(3-methoxyphenyl)-pyrrolo[2,3-d]pyrimidine

Example 59: 4-Amino-7-cyclobutyl-5-(4-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine, m.p.: 224-226°C

Example 60: 4-Amino-7-cyclobutyl-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidine, m.p.: 236-238°C

Example 61: 4-Amino-7-cyclobutyl-5-(3-methoxyphenyl)-pyrrolo[2,3-d]pyrimidine, m.p.: 167-169°C

Example 62: 2-(4-Amino-5-(4-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexanol

Example 63: 2-(4-Amino-5-(3-hydroxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexanol

Example 64: 2-(4-Amino-5-(3-methoxyphenyl)-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexanol

Example 65: Acetic acid-2-acetoxy-4-(4-amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-(1,4/2)-cyclopentyl ester, m.p.: 154-157°C

Example 66: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-(1,4/2)-cyclopentane-1,2-diol, m.p.: 140-145°C

Example 67: 3-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclobutanecarboxylic acid ethyl ester, m.p.: 136-142°C

Example 68: 7-Cyclobutyl-5-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine, m.p.: 165-167°C

Example 69: *cis*-3-[4-Amino-5-(3-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutane-carboxylic acid methyl ester, m.p.: 233-236°C

Example 70: *trans*-3-[4-Amino-5-(3-hydroxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutanecarboxylic acid methyl ester, m.p.: 176-180°C

Example 71: 3-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutane-carboxylic acid methyl ester, m.p.: 159-161°C

Example 72: {3-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclobutyl}-methanol, m.p.: 151-153°C

Example 73: 7-Cycloheptyl-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p.: 146-148°C

The following are prepared analogously to Example 36:

Example 74: 4-[4-Amino-5-(3-methoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclohexanol, m.p.: 191-193°C

Example 75: 7-Cyclohexyl-5-(3-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p.: 146-148°C

Example 76: 4-(4-Amino-5-phenyl-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclohexanol, m.p.: 198-200°C

Examples A-B: Pharmaceutical compositions

Example A: Tablets each comprising 50 mg of active ingredient:

Composition (10 000 tablets)	
active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silica (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of the potato starch and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remaining potato starch, the magnesium stearate, the talc and the silica

are mixed in and the mixture is compressed to form tablets each weighing 145 mg and comprising 50 mg of active ingredient, which may, if desired, be provided with dividing notches for finer adaptation of the dose.

Example B: Film-coated tablets, each comprising 100 mg of active ingredient:

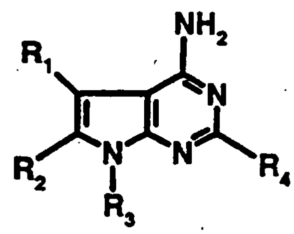
Composition (1000 film-coated tablets)

active ingredient	100.0 g
lactose	100.0 g
corn starch	70.0 g
talc	8.5 g
calcium stearate	1.5 g
hydroxypropylmethylcellulose	2.36 g
shellac	0.64 g
water	q.s.
dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed, and the mixture is moistened with a paste, prepared from 15 g of the corn starch and water (with heating), and granulated. The granules are dried, and the remaining corn starch, the talc and the calcium stearate are mixed with the granules. The mixture is compressed to form tablets (each weighing 280 mg), which are then coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of each film-coated tablet: 283 mg).

What is claimed is:

1. A compound of formula I



(I)

wherein

R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;

or a salt thereof.

2. A compound of formula I according to claim 1, wherein

R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;

or a salt thereof.

3. A compound of formula I according to claim 1, wherein

R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;

R_2 and R_4 are hydrogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;

or a salt thereof.

4. A compound of formula I according to claim 1, wherein

R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1-C_3-alkylenedioxy, cyano and halogen;

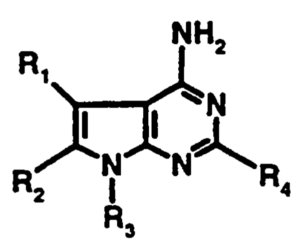
R_2 and R_4 are hydrogen; and

R_3 is unsubstituted or substituted cyclopropyl, cyclopentyl, cyclopentenyl or cyclohexyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl;

or a pharmaceutically acceptable salt thereof.

5. The use of a compound of formula I



(I)

wherein

R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl;
or of a pharmaceutically acceptable salt thereof,
in the preparation of a medicament for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase pp60$^{c\text{-}src}$.

6. The use according to claim 5, wherein a compound of formula I wherein
R_1 is aryl;
R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and
R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,
with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl and hydrocarbyloxycarbonylamino-alkyl;
or a pharmaceutically acceptable salt thereof, is used.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and at least one pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 4 for use in a method for the therapeutic treatment of the animal or human body.

9. A compound according to any one of claims 1 to 4 for use in the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase pp60$^{c\text{-}src}$.

10. The use of a compound according to any one of claims 1 to 4 in the preparation of a pharmaceutical composition.

11. The use of a compound according to any one of claims 1 to 4 in the preparation of a pharmaceutical composition for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase pp60$^{c\text{-}src}$.

and, if desired, converting a compound of formula I into a different compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into a different salt, and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.